ZJW
AF

Atty. Docket No. TAK03 P-323

CERTIFICATE OF MAILING

I hereby certify that this paper, together with all enclosures identified herein, are being deposited with the United States Postal Service as first class mail, addressed to the Mail Stop Appeal Brief - Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450, on the date indicated below.

June 12, 2006
Date

Deborah A. Clark
Deborah A. Clark

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Art Unit	:	1651
Examiner	:	Francisco C. Prats
Appln. No.	:	10/018,770
Applicants	:	Yoshihito Ikeda et al.
Filing Date	:	December 17, 2001
Confirmation No.	:	2012
For	:	DRUG COMPOSITION CONTAINING A LECITHIN-MODIFIED SUPEROXIDE DISMUTASE

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

TRANSMITTAL OFAPPELLANTS' REPLY UNDER 37 CFR §41.41

Enclosed herewith is the Appellant's Reply Brief for the above-identified application.

If any fees are required, please charge to Deposit Account No. 16-2463. A duplicate of this transmittal is attached.

Respectfully submitted,

YOSHIHITO IKEDA ET AL.

By: Price, Heneveld, Cooper,
DeWitt & Litton, LLP

June 12, 2006
Date

Gunther J. Evanina
Gunther J. Evanina, Registration No. 35 502
695 Kenmoor, S.E./Post Office Box 2567
Grand Rapids, Michigan 49501
(616) 949-9610

GJE/dac

Atty. Docket No. TAK03 P-323

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Art Unit	:	1651
Examiner	:	Francisco C. Prats
Appln. No.	:	10/018,770
Applicants	:	Yoshihito Ikeda et al.
Filing Date	:	December 17, 2001
Confirmation No.	:	2012
For	:	DRUG COMPOSITION CONTAINING A LECITHIN-MODIFIED SUPEROXIDE DISMUTASE

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sirs:

APPELLANTS' REPLY UNDER 37 CFR §41.41

This Reply Brief addresses new points of argument raised in the Examiner's Answer mailed May 1, 2006.

SUMMARY

The rejection of Appellants' claims are based on the assumption that the JP '882 reference teaches that disaccharides, such as sucrose, are effective for stabilizing SOD (underivitized superoxide dismutase) against all forms of degradation, and that SOD and PC-SOD (lecithin-modified superoxide dismutase) would be expected to have identical degradation issues. Both of these assumptions are inconsistent with the prior art. The JP '882 reference teaches that SOD does not require stabilization against denaturation during lyophilization, and that the only purpose for utilizing a disaccharide, such as sucrose, during lyophilization of SOD is to prevent dimerization of the SOD and allergenic side effects associated with administration of the dimer. U.S. Patent No. 5,762,929 teaches that there are not any allergenic side effects associated with administration of PC-SOD. Therefore, there is no motivation in the prior art for adding sucrose to PC-SOD during lyophilization. It is only

through selective ignorance of these facts and/or by reference to Appellants' own disclosure, that Appellants' claimed invention can be reconstructed from the prior art.

The claimed invention involves the use of sucrose to prevent degradation of the PC moieties, a problem that is non-existent with underivatized SOD, and which is completely unrelated to the problems associated with underivatized SOD dimerization and the accompanying allergenic side effects. The prior art does not teach or suggest the claimed invention, and does not provide motivation for adding sucrose to lecithinized superoxide dismutase (PC-SOD) to prevent degradation and loss of activity associated with breakage of bonds in the lecithin moieties.

Reply To New Points Of Argument Raised In The Examiner's Answer

The Examiner has argued that the Board of Patent Appeals and Interferences is required to affirm the Examiner's finding of obviousness because "[a] reasonable expectation of success would have been based on the fact that JP '882 discloses that the very same enzyme was rendered storage stable by combination with sucrose."

However, PC-SOD and SOD are not the very same thing, and, as taught by the prior art of record, PC-modified SOD has very different properties from SOD. Most importantly, unlike SOD, which, according to the prior art, requires stabilization against dimerization because of problems relating to allergenic side effects, the prior art (U.S. Patent No. 5,762,929 at column 1, lines 59-61) discloses that PC-SOD can be administered to a patient "without adverse effect such as antigenicity." This means that PC-SOD does not have the allergenic side-effects associated with dimerization of SOD as reported by JP '882. This alone is a very substantial difference between PC-SOD and SOD, which undermines the Examiner's argument that PC-SOD and SOD are essentially the same, and have essentially the same properties.

The Examiner argues that Appellants bear the burden of demonstrating non-obviousness. It is of course the Examiner's burden to first establish *prima facie* obviousness. This has not been done with respect to the claims at issue. When applying 35 U.S.C. §103, the references must be considered as a whole and must suggest the desirably of the claimed

invention. *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n. 5, 229 USPQ 182, 181 n.5 (Fed. Cir. 1986). One having ordinary skill in the art would not have been motivated by the JP '882 reference to use sucrose to stabilize PC-SOD against dimerization to avoid allergenic side effects, since the prior art (5,762,929) discloses that administration of PC-SOD does not cause allergenic side effects. The relatedness of PC-SOD to SOD (PC-SOD being a lecithin derivatized form of SOD) does not change the fact that the prior art teaches that the problems motivating stabilization of SOD (allergenic side effects associated with dimerization) are not present with PC-SOD. To find obviousness based on the facts in this case, it is necessary to ignore the relevant law by disregarding the teachings of the prior art as a whole, and/or come to the illogical conclusion that a person of ordinary skill in the relevant art would have found it obvious to attempt to solve a problem that is non-existent according to the prior art (the '929 patent). A person of ordinary skill in the art would not have been motivated to use sucrose to prevent allergenic side effects by inhibiting dimerization of PC-SOD based on the teachings of the JP '822 reference in view of U.S. Patent No. 5,762,929 which discloses that PC-SOD does not have the allergenic effects of underivatized SOD addressed by JP '882.

The Examiner argues that the rejection is proper because JP '882 clearly discloses that the purpose of combining sucrose with underivatized SOD is to avoid denaturation. This is not entirely correct. The JP '882 reference states that U.S. Patent No. 3,637,642 (actually U.S. Patent No. 3,637,640) reports that denaturation of bovine SOD is 25% or greater with freeze-drying, but that by combining pentose and hexose with bovine SOD prior to freeze-drying, denaturation of bovine SOD is prevented. This discussion of the prior art in the JP '882 reference does not change the fact that the JP '882 reference reports that denaturation of human SOD does not occur during multiple freeze-frost cycles, and that the disclosed purpose of adding sucrose to SOD is to prevent dimerization (the chemical combination of two monomers) of SOD and the associated allergenic side effects, not to prevent denaturation (which is the uncoiling of the SOD into an inactive conformation). The JP '882 reference warns that while certain other compounds (e.g., arabinose, glucose and galactose) are effective for preventing dimerization (as determined by high-performance gel filtration liquid chromatography), these compounds cause denaturation, whereas substantial dimerization without denaturation occurs

when freeze-drying SOD without any additive. This information is summarized in Table 2 of the JP '882 English language translation. Comparative Examples 2-5 show that when sorbitol, mannitol, inositol, sucrose, trehalose, maltose or lactose are added, dimerization is inhibited without any accompanying denaturation. Clearly, the teachings of the JP '882 reference are directed to additions that prevent dimerization and the associated allergenic side effects that occur when freeze-dried SOD is administered to a patient, without also causing denaturation.

The JP '882 reference does not teach that bovine SOD is susceptible to denaturation, but instead only states that U.S. Patent No. 3,637,640 alleges greater than 25% denaturation of bovine SOD during freeze-drying. U.S. Patent No. 3,637,640 reports denaturation of lyophilized bovine SOD. However, this patent does not provide a credible teaching regarding bovine SOD susceptibility to denaturation. First, the '640 patent itself discloses that the degree of denaturation is determined by "[a]bsorbance values at 280 mμ" (column 5, lines 32-45), but that a reliable determination of the absorbance value at 280 mμ for orgotein (bovine SOD) without a stabilizer "is not possible because of the presence of insoluble flakes in the turbid solution." This suggests that the degree of denaturation of lyophilized bovine SOD without a stabilizer was not actually determined. There is nothing in the JP '882 reference to suggest that bovine SOD is any more or less susceptible to denaturation during lyophilization than human SOD, which the JP '882 reference reports is stable against denaturation during lyophilization. The Examiner's arguments rest on the disproven assumption that SOD and PC-SOD would be expected to behave substantially the same way. Applying this reasoning to the contradictory facts asserted in the JP '882 reference, it must be presumed that bovine SOD and human SOD also behave similarly, since these are very similar compounds, and as shown by the JP '882 reference, are not susceptible to denaturation during lyophilization. In addition, the reported susceptibility of bovine SOD to denaturation (in U.S. Patent No. 3,637,640) is in direct conflict with the teachings of U.S. Patent No. 4,346,174, which reports that "bovine erythrocyte superoxide dismutase is very resistant to denaturation." Overwhelmingly, the prior art is teaching that denaturation of SOD during lyophilization is not a problem in the absence of a stabilizer, but that certain stabilizers used to prevent dimerization, not denaturation, unfortunately cause denaturation. It is illogical to expect that those having

ordinary skill in the art would be motivated to add sucrose to PC-SOD to solve a nonexistent problem with PC-SOD (i.e., dimerization and the associated allergenic side effects) merely because it does not cause denaturation.

The Examiner argues that because the JP '882 reference discloses that "sucrose is a better preservative for human SOD than arabinose, glucose and galactose, [the JP '882 reference] provides motivation for using sucrose as a stabilizer in freeze-dried storage applications for the PC-SOD disclosed in JP '729, the PC-SOD of JP '729 being the same enzyme as the SOD of JP '882, except for the lecithin moiety attached thereto."

This line of reasoning fails to consider the teachings of the references as a whole. It ignores the fact that PC-SOD is different with respect to allergenic effects. The JP '882 reference teaches prevention of dimerization of SOD and the associated allergenic side effects, not prevention of dimerization of PC-SOD. U.S. Patent No. 5,762,929 reports that the biologically active PC-SOD does not have allergenic effects associated with its administration to patients. Accordingly, based on the teachings of the prior art as a whole, the person of ordinary skill in the art would not be motivated to stabilize PC-SOD against dimerization to prevent a non-existent allergenic effect.

The Examiner argues that it is a fact that the JP '882 reference is using sucrose to prevent desirable active dimers of the underivatized SOD enzyme from forming undesirable dimers of the desirable active dimer (i.e., tetramers). These "facts" have not been established and made of record. However, if the Examiner's unsupported allegations are taken as fact, they demonstrate that the prior art does not provide motivation for the claimed invention. Regardless of whether the JP '882 reference teaches using sucrose to stabilize SOD against tetramerization, as alleged by the Examiner, or against dimerization, as actually stated in the JP '882 reference, it is for the purpose of preventing the formation of chemical reaction products having an allergenic effect. However, there is nothing in the prior art suggesting that PC-SOD is susceptible to the formation of reaction products having an allergenic effect. Instead, the prior art (U.S. Patent No. 5,762,929) teaches that administration of PC-SOD does not cause allergenic side effects, thereby removing motivation for stabilizing PC-SOD with

sucrose. Based on the prior art, it is totally unpredictable that sucrose would be effective to stabilize lyophilized PC-SOD against degradation of the PC moieties.

While the Examiner is correct in stating that the JP '882 reference does not disclose that sucrose promotes degradation of underivatized SOD, there is no motivation for employing sucrose as a stabilizing agent for PC-SOD. The prior art establishes that administration of PC-SOD does not cause the allergenic side effects of the type reported by the JP '882 reference for unstabilized SOD.

The Examiner argues that Appellants have not provided a solution to an undiscovered problem, since Appellants' specification states that the prior art have not solved problems attendant with long-term storage and lyophilization of PC-SOD. This argument ignores the fact that storage problems relating to dimerization (or tetramerization, as suggested by the Examiner) of underivatized SOD, and denaturation of underivatized SOD (which the JP '882 reference reports as nonexistent) are not the same as the previously unrecognized problem of PC moiety degradation of PC-SOD. The fact that sucrose stabilizes SOD against dimerization does not suggest that sucrose will stabilize PC-SOD against degradation of the PC moieties.

The Examiner argues that stabilization of PC-SOD is no different from stabilization of SOD since they are nearly identical molecules with identical enzymatic activity. This argument ignores the fact that PC-SOD does not have the same stability problems of SOD. The stability problems with PC-SOD are entirely different from the stability problems of SOD. With PC-SOD, the stability issue relates to degradation of the PC moieties, which are not present in underivatized SOD. The stability issue with underivatized SOD relates to dimerization and the associated allergenic side effects, a problem which the prior art teaches is nonexistent with PC-SOD.

The Examiner admits that U.S. Patent No. 5,762,929 does not disclose any stability problems with PC-SOD. It, in fact, teaches that administration of PC-SOD does not have the undesirable allergenic side effects associated with dimerization of SOD. Nevertheless, the Examiner argues that none of this is relevant to patentability because the '929 patent does not directly address long-term storage of PC-SOD in freeze-dried form. This is incorrect. The examples in the '929 patent pertain to lyophilized (freeze-dried) PC-SOD that is subsequently

incorporated into tablets or capsules, which are inherently intended to be shipped and stored prior to use.

The Examiner argues that the '929 patent "does provide credence to the suggestion that the preservatives for SOD disclosed by JP '882 should also be used with PC-SOD, since the '929 patent discloses the use of mannitol as an excipient in an injectable liquid and lactose as a tablet excipient." The '929 patent does not disclose that mannitol or lactose (which are not claimed) are used as stabilizers, but instead suggests that these disaccharides are employed for entirely different reasons. It would be understood by a person of ordinary skill in the art that the PC-SOD is dissolved in a 5% mannitol solution (Example 2-1) to provide an injectable solution having a suitable isotonicity. This is abundantly clear from the statement that "[t]he osmotic pressure ratio of the solution against physiological saline solution was about 1" (see column 7, lines 44-53, which refer to dissolving PC-SOD in a 5% mannitol aqueous solution). Similarly, those having ordinary skill in the art would not find any suggestion that the lactose excipient used in Example 2-2 is intended to stabilize PC-SOD. Lactose is one of the most commonly employed filler/binder excipients used in solid pharmaceutical dosage forms. The use of lactose in this context does not suggest the use of sucrose to stabilize PC-SOD.

Appellants admit misstating that the prior art shows that a substance expected to inhibit dimerization would be expected to shift the equilibrium distribution of PC-SOD toward its monomeric form and one step closer to denaturation. This was an inadvertent reference to a recent (non-prior art) publication forwarded to the Examiner (but not made of record) showing the relationship between SOD and its dimerized, monomer and denatured forms. Regardless of whether facts tending to show this relationship are admissible in this proceeding, the applied prior art (JP '882) suggests the use of sucrose to prevent allergenic effects associated with administration of lyophilized SOD to a patient, which the '929 patent states is not a problem with PC-SOD.

The Examiner argues that since the difference between PC-SOD and SOD is only as little as an 800 Dalton phosphatidylcholine group bonded to a 40,000 Dalton protein, "a person of ordinary skill in the art would have expected the physical properties of PC-SOD to have been fairly similar to the physical properties [of] the underivitized SOD," and "would not have

ignored prior art disclosing ingredients advantageous in lyophilized forms of the closely related compound SOD."

Appellants are not arguing that the JP '882 reference should be ignored. To the contrary, Appellants are arguing that it and the '929 patent should be considered for everything they teach. This includes the purpose of using sucrose to stabilize SOD against the formation of dimers having an allergenic side effect, and the disclosure that administration of PC-SOD does not cause allergenic side effects. When these facts are considered, there is no motivation for using sucrose to stabilize PC-SOD.

The Examiner agues that "[r]eading JP '882 as somehow disclosing that sucrose promotes the degradation of the underivatized enzyme is to ignore the basic thrust of the disclosure therein." Yet, the Examiner is ignoring the fact that the JP '882 patent is teaching the use of sucrose and other disaccharides as a stabilizer to prevent dimerization and the associated allergenic side effects caused by administering dimerized SOD to patients. The Examiner is also ignoring the fact that the U.S. Patent No. 5,762,929 teaches that there are no allergenic side effects associated with administering PC-SOD to patients. Accordingly, the prior art is teaching that the reason for using sucrose for stabilizing SOD is not relevant to PC-SOD. Should these facts be ignored?

The Examiner argues that Appellants have stated "that PC-SOD differs from SOD with respect to its distribution in the living body, and affinity to self," etc., but that "appellant fails to support any of these assertions with any direct evidence." This is incorrect. Appellants submitted the *Journal of Pharmacological and Experimental Therapeutics*, Vol. 262, No. 3, p. 1214-1219 (1992), which describes that lecithinized SOD (PC-SOD) has a Forssman antiserum-induced effect, delayed disappearance in plasma as compared with SOD, 4 to 20 times higher cell affinity and 200 times or more pharmacological potency than SOD. More importantly, Appellants submitted U.S. Patent No. 5,762,929 which teaches that administration of PC-SOD to a patient does not cause allergenic side effects associated with dimerization of SOD, and therefore does not require stabilization against dimerization as taught by JP '882.

The Examiner argues that Appellants' statement that they discovered a loss of biological activity of PC-SOD during freeze-drying and/or freeze-thawing cycles due only to degradation of the phosphatidylcholine moieties is not supported by the disclosure, and is contrary to Appellants' specification which, according to the Examiner states that "the prior art had not solved the problems attendant with long-term storage and lyophilization of PC-SOD." However, Appellants' statement is entirely consistent with its own disclosure and with the prior art. The only known degradation issues with underivatized SOD are denaturation and dimerization. However, the JP '882 reference teaches that denaturation of lyophilized SOD occurs only when certain stabilizers (e.g., arabinose, glucose and galactose) are added. Further, the JP '882 reference does not teach that dimerization causes a loss of activity, but instead causes the formation of a product having allergenic side effects. U.S. Patent No. 5,762,929 teaches that there are not any allergenic side effects associated with administration of PC-SOD. Thus, in the absence of stabilizers, there are not any expected degradation products which would lead to loss of activity (e.g., denaturation) or allergenic effects (dimerization). Accordingly, the reduction of activity of PC-SOD due to long-term storage referenced in Appellants' specification is entirely attributable to degradation of the PC moieties. This is demonstrated in Example 1 of Appellants' specification which indicates (at page 32) that the use of sucrose in accordance with the invention provides an extremely stable lyophilized composition (significantly smaller reduction of enzymatic activity) which is correlated with a reduction in degradation products formed by the breaking of bonds in the PC moieties. This demonstrates a causal relationship between degradation of PC moieties and PC-SOD loss of activity. Appellants have discovered a solution to a previously unrecognized problem, i.e., loss of activity associated with degradation of PC moieties of PC-SOD. The prior art references, when considered as a whole, do not suggest stabilization of PC-SOD with disaccharides such as sucrose, since the motivation for using disaccharides as a stabilizer to prevent dimerization of SOD and the associated allergenic side effects are nonexistent with PC-SOD.

Finally, the Examiner argues that hindsight reasoning is necessary to reconstruct Appellants' claimed invention. Nevertheless, the Examiner believes that such hindsight

analysis is appropriate "so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure." However, a person of ordinary skill in the art considering only what is known from the prior art, and not taught by Appellants, would have discovered that JP '882 is teaching the addition of disaccharides to stabilize SOD against dimerization to prevent allergenic side effects, and that U.S. Patent No. 5,762,929 teaches that PC-SOD does not have such allergenic side effects. Therefore, the person of ordinary skill in the art would not have been motivated to use sucrose to stabilize PC-SOD. It is respectfully submitted that the person of ordinary skill in the art cannot learn from the prior art that loss of activity associated with lyophilization and storage of PC-SOD is caused by degradation of the PC moieties, or that such degradation is prevented by adding sucrose. These facts, and the entire motivation for the claimed invention, can only be found in Appellants' specification, not in the prior art.

CONCLUSION

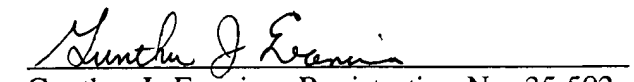
For the reason stated above, it is respectfully submitted that a *prima facie* case of obviousness has not been established. Accordingly, Appellants request a reversal of the rejection.

Respectfully submitted,

YOSHIHITO IKEDA ET AL.

By: Price, Heneveld, Cooper,
DeWitt & Litton, LLP

June 12, 2006
Date



Gunther J. Evanina, Registration No. 35 502
695 Kenmoor, S.E./Post Office Box 2567
Grand Rapids, Michigan 49501
(616) 949-9610

GJE/dac